

# Periodic Fever

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.*

**DR. HOWARD MORRELLI\*:** The patient is a 33-year-old Caucasian housewife and hairdresser from Sacramento, California. She was admitted to the University of California Hospital because of recurrent chills and fever of lifelong duration. As a child, she had had intermittent fever of 39.4° to 40°C (103° to 104°F) every four to six weeks which was attributed to respiratory infections. As she grew older, these episodes became more frequent and more severe. At present, every 10 to 14 days she has fever of 39.4° to 40°C, occasionally as high as 41°C (106°F), lasting three to four days. During these episodes she has noticed tenderness and swelling of lymph nodes. On biopsy of one of the nodes a year before the present admission, non-specific lymphadenitis was noted. Occasionally with these critical episodes, the patient has had sharp abdominal pain, headaches or dysphagia. At the end of an attack she frequently has noticed diarrhea. She thinks that her father may have had a similar affliction. Both of her children have a similar problem in that every four to six weeks they have a fever of 40° to 41°C (104° to 106°F) lasting 24 hours.

On physical examination, rectal temperature was 38°C. Several discrete, slightly tender axillary, inguinal and cervical lymph nodes were felt. Results of examination of the chest, heart and abdomen were within normal limits.

The number and the types of leukocytes in the blood were within normal limits, the hematocrit was 36 per cent, and the erythrocyte sedimentation rate, uncorrected, 51 mm in one hour. Urinalysis showed a trace of protein, but a 24-hour collection revealed less than 100 mg of protein per 100 ml. Serum protein electrophoresis demonstrated slight elevation in alpha-2-globulins and gamma globulins. Serum fibrinogen during a febrile episode was elevated to 581 mg per 100 ml. Determination of urinary etiocholanolone excretion was done inde-

pendently in two laboratories on two separate days when the patient was febrile, and in both instances the amount reported was at the lower end of normal range.

An x-ray film of the chest showed slight prominence of the main pulmonary artery. Antinuclear antibodies and febrile agglutinins, and results of renal function and liver function tests were all within normal limits. Blood volume studies by the Evans blue method, the iodinated albumin method and chromium-labeled blood cell techniques were normal, indicating no discrepant uptake of dye which might indicate systemic amyloidosis. The absence of amyloidosis was further substantiated by rectal biopsy.

By the fourth hospital day the patient was afebrile. (The highest level the temperature had reached was 39°C. She was discharged on a 20-gm fat diet in the hope that this might ameliorate the symptoms. Although febrile episodes recurred at 10- to 14-day intervals, the temperature would reach only 38.4°C (101°F) rather than 39.4° to 40°C (103° to 104°F), but the patient did not think the improvement in symptoms warranted the very restrictive 20-gm fat diet.

**DR. LLOYD H. SMITH, JR.\*1:** How are you feeling today?

**PATIENT:** Very good.

**DR. SMITH:** Could you describe for the doctors here what happens when one of these attacks begins?

**PATIENT:** I feel very cold at first, and I shake. I have a fever while I am cold.

**DR. SMITH:** How long does it last?

**PATIENT:** About three days. I don't think it has ever lasted longer than that.

**DR. SMITH:** Does it really incapacitate you? Do

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you have to go to bed and give up your ordinary activities?

PATIENT: Sometimes I do; not all the time. It depends on the height of the fever.

DR. SMITH: Are you bothered by pain in your abdomen or in your chest? Do you have difficulty breathing when you have these attacks?

PATIENT: No, just headaches; or sometimes aching in the stomach or abdomen.

DR. SMITH: You were put on a low fat diet after your visit here. Do you believe this gave you any improvement in the frequency or the severity of these attacks?

PATIENT: I think they happened just as often. The fevers didn't get as high.

UNKNOWN PHYSICIAN IN AUDIENCE: What is the patient's family background?

DR. SMITH: Do you want to describe the origin of your family?

PATIENT: My father was born in Rome. He died when I was 10. My mother is 77 and very healthy.

DR. SMITH: Where was she from originally?

PATIENT: She was born in South Dakota.

DR. SMITH: Thank you very much for coming in this morning. (The patient leaves.) Now I will ask Dr. Morrelli, who has been interested in this syndrome, to review it for us.

DR. MORRELLI: The patient has a very rare disease; only 275 cases have been reported in the literature through 1964. It was first characterized clearly by Janeway<sup>7</sup> in 1908 and I think his description of a young girl with paroxysmal peritonitis is the best available in literature. It was recognized at this hospital by Althausen in 1930, and a case report was written describing it as the "false acute abdomen." Beginning in the 1940's, large series of cases began to appear in the literature, the disease variously called benign paroxysmal peritonitis, periodic disease, familial Mediterranean fever and familial recurrent polyserositis. There is no clearly defined etiologic explanation for the disease. As will be emphasized later, it is probably genetic, transmitted either as an autosomal dominant with incomplete penetrance or a recessive trait. Since we have no means of substantiating this etiologic conjecture by means of a specific laboratory test, it is at this time a symptom complex only.

## Clinical Features

The symptom complex consists of episodes of recurrent fever. The fever is not an equivocal or trivial fever but usually is in the range of 39.4° to 40°C (103° to 104°F), occasionally reaching 41° (106°). It is always reported to be periodic, the patients reporting variously that they have fever once a month or once every seven days; but when an accurate log is kept, it is found that in an individual case the fever has a variation within the time period that the patient has related. The disease is ordinarily of such long duration that serious diseases such as tuberculosis and lymphoma can be excluded. In addition to the fever, the patients most commonly have pain, particularly severe abdominal pain, characteristic of peritonitis. Early in the history of this disease, most patients have had an appendectomy or cholecystectomy because of the pronounced signs of peritoneal irritation, fever and leukocytosis which are characteristic of the syndrome. A large number of patients have stethalgia or chest pain of a pleuritic nature. On x-ray examination there may be evidence of a small pleural effusion or disc atelectasis on the involved side. The arthritis of familial Mediterranean fever is less impressive, both numerically and as an individual symptom. The joints do not usually seem to be as severely involved as in gout or rheumatoid arthritis. During the asymptomatic intervals, the patient is perfectly well—as the patient was today—and in this respect an analogy can be drawn between periodic fever and gout: In the intercritical periods, a patient with either disease might well run in the Olympic Games.

No pathologic state is found after exhaustive examination that would account for the symptoms. The patients have recurrent attacks at intervals from once a year to once a week. In any given individual, this interval is fairly characteristic. During the course of the disease, the interval tends to shorten; however, the intervals may become longer and spontaneous remissions may occur. In recent years, it has become apparent that in a fair number of patients with this disease amyloidosis develops, and they may die of renal failure.<sup>4,17</sup> Unfortunately, there has been no constant relationship between the clinical manifestations in a given patient and the likelihood that amyloidosis will develop.

Table 1 is a summary of the clinical features in patients reported in the literature through 1964. There are three major reviews: By Heller in 1958,<sup>8</sup> by Ehrenfeld in 1961,<sup>3</sup> and by Siegal in 1964.<sup>15</sup>

TABLE 1.—Frequency of Signs and Symptoms of "Familial Mediterranean Fever"

	Heller 1958	Ehrenfeld 1961	Collected '30 to '62	Siegal 1964	Totals	Per Cent
Number of patients.....	74	55	92	50	271	.....
Fever.....	74	55	92	50	271	100
Abdominal pain.....	68 (92)	34 (62)	88 (96)	49 (98)	239	88
Chest pain.....	60 (81)	21 (38)	42 (45)	41 (82)	164	60
Joint pain.....	61 (82)	17 (31)	56 (61)	22 (44)	156	57
Erysipeloid.....	27 (36)	4 (7.2)	4 (4.3)	4 (8)	39	14
Positive family history.....	42 (57)	16 (29)	41 (44)	14 (28)	113	42
Leukocytosis.....	Usual	Usual	Usual	47	.....	.....
Sedimentation rate decidedly elevated.....	Usual	Usual	Usual	35 per cent	.....	.....
Jewish.....	73 (98)	55 (100)	60 (66)	38 (76)	226	83
Mediterranean.....	74 (100)	55 (100)	65 (70)	12 (24)	206	76
Proven amyloid.....	3	4	20 (most recent)	1 (2)	28	12
Men/women.....	50/24	36/19	59/33	36/14	181/90	.....
Age at Onset						
1- 9.....	46	14	.....	12	72	Prepon-
10-19.....	27	17	.....	19	63	derance
20-29.....	1	13	.....	14	28	of onset
30-39.....	0	7	.....	4	11	at less than 20 years

Fever was the universal complaint. In the combined group the incidence of abdominal pain, characteristic of peritonitis, was 88 per cent. Chest pain occurred in 60 per cent of the patients, joint pain in 57 per cent.

Heller's article in 1958 described an erysipeloid lesion of the lower extremities in 27 of 74 patients. However, observers reporting since then have found this to be a fairly infrequent manifestation of the disease—the overall incidence 14 per cent. Similarly, with regard to the family history, if collected by an observer who sees family members from a small local geographic area, familial incidence of the disease will be considerably higher than that shown in a combination of individual case reports.

Leukocytosis, between 10,000 and 20,000 per cu mm of blood, is expected. The erythrocyte sedimentation rate is usually quite high, commonly between 50 and 75 mm in an hour.

The first two series by Heller and Ehrenfeld are possibly skewed toward a very high incidence among the Jewish population. At one time there was a great concern about the relative preponderance of occurrence in Sephardim amongst the Jews, but this has not proved to be of great diagnostic importance. In the remainder of the case reports an inordinately high proportion of patients are Jews, but there is also a significant proportion of Armenians and Italians. The same can now be said also of peoples remote from Mediterranean origin. Because the first review articles were published from the Mediterranean area, it was felt

that all patients were Mediterranean; hence the epithet *familial Mediterranean fever*. In later publications, it has become quite clear that this is not the case.

About twice as many men as women have been reported with this disease. Proven amyloidosis in these patients was infrequently recognized early, but in the later case reports it has become apparent that amyloidosis is a significant complication of the illness, and may appear very early. In recent years the reported incidence of amyloidosis has become higher.

Additional symptoms that are mentioned with some frequency in the review articles and case reports are constipation, vomiting, disturbances in micturition, severe headaches—periodic meningitis as a manifestation of this disease has been reported<sup>5</sup>—diarrhea and, sometimes, precordial pain. There is only one documented case in which precordial pain was simultaneous with electrocardiographic changes of pericarditis. Sialorrhea has been reported; profuse diaphoresis with the termination of the attack is characteristic. As a manifestation of serous membrane involvement the serous membranes of the testes may be affected, causing testicular pain. Lymphadenopathy is not frequently described in the syndrome, but certainly it was a prominent feature in the patient presented today. Splenomegaly is occasionally reported.

An interesting physical finding described in 1961<sup>11</sup> was an increased incidence of cystic degeneration of the elastic lamina of Bruck. On ex-

amination of the choroid, a "domino" appearance was seen. I have not seen later reports confirming this as a frequent finding in Mediterranean fever. As mentioned earlier, the symptoms have usually been present for many years before the diagnosis is established. This is helpful in establishing the diagnosis. Table 2 outlines the data of Heller and Ehrenfeld<sup>3,6</sup> indicating that the disease has commonly been present for many years before diagnosis is made.

At laparotomy or peritoneoscopy, the gross appearance of the serosal membranes is that of edema and hyperemia. On biopsy, or if the appendix is removed, one sees edema and bland infiltration with mononuclear, plasma and mast cells.<sup>18</sup> Fibrillar change in collagen has been described in some cases.

### Treatment

I would like to expound on the pathological physiology and the rational approach to drug therapy of this disorder but I am unable to do that, since the basic physiologic disturbance is unknown. The treatment is generally symptomatic—aspirin for the fever, usually partially effective, meperidine (Demerol®) or morphine for severe painful episodes. (Narcotic addiction is uncommon in this condition.) The 20-gm fat diet recommended by Mellinkoff<sup>9,10</sup> is probably worthy of trial pending definitive etiologic knowledge. Antihistamines, antibiotics, corticosteroids, antiepileptic agents, sympathetic blocking agents, antimalarial drugs, ergotamine, paraminobenzoic acid, ephedrine, phenylbutazone, phenothiazines, atropine and appendectomy are all unsuccessful in therapy. This disease is so chronic and recurrent that it leads physicians to try many drugs seriatim in an attempt to ameliorate the symptoms.

TABLE 2.—Duration of Symptoms in 129 Cases of "Familial Mediterranean Fever" at Time of Diagnosis (Heller and Ehrenfeld)

	Number of Cases
1- 4 years .....	24
5- 9 years .....	48
10-14 years .....	26
15-19 years .....	14
20-24 years .....	8
25 and more .....	9

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### Etiology

The causes postulated for this illness are numerous. A genetic basis has been suggested<sup>13,16</sup> but there is no objective proof for this. Since the original case reports were from the Mediterranean area, it was suspected that there might be an agent in the environment which caused the symptoms. An analogous situation is now coming about in the etiologic conjectures about Burkett's lymphoma in Africa. Infection and infestation are always attractive but no etiologic agent has been found. Allergic sensitivity is sometimes mentioned as a possibility, but there have been only one or two case reports in which patients were greatly improved by being on a milk-free diet.

Physical agents have been suggested (analogous to, say, the aggravation of porphyria cutanea tarda by sunlight). Chemical agents such as pronestyl may induce a lupus-like syndrome, but there has been no unifying historical exposure to either physical or chemical agents that would permit us to explain this syndrome on these bases.

Etiocolanolone fever<sup>1</sup> was thought to be identical with familial Mediterranean fever for a very short time—until a number of patients with the latter were found to have normal etiocolanolone excretion rates. Neoplastic diseases have been suggested as a possibility, since myeloma may be complicated by amyloidosis and since Hodgkin's may present as fever, but I find no closer relationship than these symptomatic examples. The degenerative diseases probably do not pertain here, since the disease begins as a rule early in childhood; about 75 per cent of patients have symptoms before age 20. In the middle 1940's there was discussion attributing the disease to some periodic or natural rhythm of the body itself.<sup>14</sup> This has not withstood the test of time. I have included as reference<sup>12</sup> a bit of interesting reading about periodicity as a cause of the disease. It is a very lengthy expostulation on host factors that might cause symptoms to recur in a periodic fashion. These theories attempted to explain the periodic fever of malaria, the cause and pathogenesis being then unknown.

DR. SMITH: I think Dr. Morrelli has covered all the pertinent information now available concerning this very distressing and mysterious illness. Are there any questions?

DR. OTTO GUTTENTAG\*<sup>2</sup>: Would you mind elaborating on the etiocolanolone findings in the patient presented today?

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DR. MORELLI: Etiocolanolone fever was found in a young man who had periodic fever. His etiocholanolone excretion rate was high. On injection of etiocholanolone into this patient, he had febrile episodes. He did not, however, have the other concomitants of Mediterranean fever nor have the other patients with proven etiocholanolone fever had peritonitis, chest pain or arthritis. Why today's patient had low etiocholanolone levels on two occasions as determined by independent laboratories is unexplained. One laboratory reported that perhaps there was an interfering substance, but did not specify what it might be.

DR. SMITH: How well has the inheritance of this disease been traced? It is quite clear that the pattern is at least vaguely that of a dominant; how much does it deviate from true dominant transmission?

DR. MORRELLI: There are families such as those in Heller's series and Ehrenfeld's series in which every generation for several generations will have a patient with the disease. Bouroncle<sup>2</sup> reported a German family in which three generations were involved, but fewer than half of all patients have a positive family history.

DR. KENNETH MELMON<sup>\*3</sup>: When I heard that the patient had edema, sialorrhea, diaphoresis, diarrhea, leukocytosis and fever, I wondered whether there is any role for the kinins in this disease?

DR. MORRELLI: We sent specimens to your laboratory for determination. The results are pending.

DR. RICHARD HAVEL<sup>\*4</sup>: You mentioned that a low fat diet was worth trying. Would you elaborate on that?

DR. MORRELLI: Mellinkoff says that it works. My limited experience is that it worked in one patient and did not work well in the second.

DR. JAMES HOPPER<sup>\*5</sup>: It is worth pointing out that although rectal biopsy is a good way to get evidence of amyloidosis, renal biopsy is probably much better.

DR. SMITH: There are other forms of familial amyloidosis. I wonder whether patients with those forms have fever. Do you know of the other types of familial amyloidosis as a comparison with this syndrome? Do the patients have amyloidosis in the absence of any plasma protein abnormality, or

do they show changes on electrophoresis or ultracentrifugation?

DR. MORRELLI: They may have minor changes in serum electrophoresis, notably an increase in alpha-2-globulin, but this is not diagnostic of the presence of amyloid. The plasma proteins may be normal by this method, and yet amyloid may be present. Ruicavina's cases of familial amyloidosis were not characterized by recurrent fever.

DR. SMITH: And yet they still have severe amyloidosis?

DR. MORRELLI: Yes.

#### GENERIC AND TRADE NAME OF DRUG

Meperidine—*Demerol*.

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